GENERAL & LOCAL ANESTHETICS

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Course: Basic Therapeutics
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EXPECTATIONS..?????
It's Quiz Time!
1. Define the term anesthesia..?
2. What are the different stages of anesthesia?
3. What are the routes of administration used for delivering general anesthetics..?
4. Mention two drugs used as general anesthetics..?
5. Mention two routes of administration for local anesthetics..?
**OBJECTIVES:**

By the end of this lecture student should be able to:

1. Define the term anesthesia.
2. Identify different stages of anesthesia.
3. Recognize types of inhaled and intravenous general anesthetics.
4. Identify different types of local anesthetics and their mechanism of action.
5. Identify effects of general anesthetics on organ systems and their toxicity.
general anaesthesia
What is a General Anesthetic?

• A drug that brings about a reversible loss of consciousness.

• These drugs are generally administered by an Anesthesiologist in order to induce or maintain general anesthesia to facilitate surgery.
Surgical Procedures Prior to Anesthesia
Background

• General anesthesia was absent until the mid-1800’s

• William Morton

\[(\text{CH}_3\text{CH}_2)_2\text{O}\]
Anesthesia

- Anesthesia = loss of sensation
- General Anesthesia = analgesia, amnesia, loss of consciousness, inhibition of sensory and autonomic reflexes and often skeletal muscle relaxation (mixture).
Hypotheses of General Anesthesia

1. **Lipid Theory:**
   based on the fact that anesthetic action is correlated with the oil/gas coefficients.
   • The higher the solubility of anesthetics is in oil, the greater is the anesthetic potency.

2. **Protein (Receptor) Theory:**
   based on the fact that anesthetic potency is correlated with the ability of anesthetics to inhibit enzymes activity of a pure, soluble protein. Also, attempts to explain the GABA\textsubscript{A} receptor is a potential target of anesthetics action.
3. **Binding theory:**
   - Anesthetics bind to hydrophobic portion of the ion channel
Mechanism of Action

UNKNOWN!!

• Most Recent Studies:
  – General Anesthetics act on the CNS by modifying the electrical activity of neurons at a molecular level by modifying functions of ION CHANNELS.
  – This may occur by anesthetic molecules binding directly to ion channels or by their disrupting the functions of molecules that maintain ion channels.
Anesthetic Suppression of Physiological Response to Surgery
• Proteins involved include:
  • Voltage-gated ion channels, such as sodium, potassium, and calcium channels.
  • Ligand-gated ion channel superfamily.
  • G protein-coupled receptors superfamily.
Essential Components of Anesthesia

- Analgesia - perception of pain eliminated
- Hypnosis - unconsciousness
- Depression of spinal motor reflexes
- Muscle relaxation

* These terms together emphasize the role of immobility and insensibility!
Stages of General Anesthesia

- **Induction**: initial entry to surgical anesthesia.
- **Maintenance**: continuous monitoring, medications to maintain depth of anesthesia, ventilation, fluid balance, hemodynamic control, homeostasis.
- **Emergence**: resumption of normal CNS function.
- **Extubation**: resumption of normal respiration.
Depth of anesthesia

- Stage I: Disorientation, altered consciousness.

- Stage II: Excitatory stage, delirium, uncontrolled movement, irregular breathing. Goal is to move through this stage as rapidly as possible.
• Stage III: Surgical anesthesia; return of regular respiration.
• Plane 1: “light” anesthesia, reflexes, swallowing reflexes.
• Plane 2: Loss of blink reflex, regular respiration (diaphragmatic and chest).
  “Surgical procedures can be performed at this stage.”
• Plane 3: Deep anesthesia. Shallow breathing, assisted ventilation needed.
  “Level of anesthesia for painful surgeries (e.g.; abdominal exploratory procedures)”
• Plane 4: Diaphragmatic respiration only, assisted ventilation is required.
• Cardiovascular impairment.
• Stage IV: Too deep; essentially an overdose and represents anesthetic crisis. This is the stage between respiratory arrest and death due to circulatory collapse.
Ideal General Anesthetic

- Induce anesthesia smoothly and rapidly and permit rapid recovery as soon as administration ceases (*Balanced Anesthesia*)
- Wide margin of safety (high therapeutic index)
- Devoid of adverse effects
General Anesthetic Protocols

• No single agent alone meets all criteria
• Combinations to maximize favorable effects and minimize unwanted effects
• Anesthetics have low therapeutic index
• **Minor Procedures**: oral sedatives and regional local anesthesia.

• **Conscious Sedation**: IV benzodiazepines and opioid analgesics (can respond to verbal commands, patent airway)

• **Major Surgical Procedures**: 
Pharmacological effects of anaesthetic agents

Anaesthesia involves three main neurophysiological changes:

- Unconsciousness.
- Loss of response to painful stimulation.
- Loss of reflexes (motor and autonomic).
Although all parts of the nervous system are affected by anaesthetic agents, the main targets appear to be the cortex, thalamus, midbrain and spinal cord.
• At supra-anaesthetic doses, all anaesthetic agents can cause death by loss of cardiovascular reflexes and respiratory paralysis.
EFFECTS ON ION CHANNELS

• $GABA_A$ receptors:
• Almost all anaesthetics (with the exceptions of cyclopropane, ketamine and xenon) potentiate the action of GABA at the $GABA_A$ receptor.
• **NMDA receptors:**

• **Glutamate**, the major excitatory neurotransmitter in the CNS, activates three main classes of ionotropic receptor-AMP, kinate and NMDA receptors. NMDA receptors are an important site of action for anaesthetics such as nitrous oxide, xenon and ketamine which act, in different ways, to reduce NMDA receptor-mediated responses.
General Anesthetics Classes

1. Intravenous
   - Injections
   - Anesthetics or induction agents

2. Inhalation
   - Gasses or Vapors
   - Usually Halogenated
Intravenous General Anesthetics
Intravenous Anesthetics

- Used in combination with inhaled anesthetics to:
  - Supplement general anesthesia.
  - Maintain general anesthesia.
  - Provide sedation.
Mechanism of action:

- Barbiturates, benzodiazepines, propofol and (ethanol) potentiate movement of Cl- ions through the GABA A receptor channel.

- Barbiturates and benzodiazepines bind at different sites on the GABA A channel.
1. Ultra-short acting Barbiturates

- *Thiopental*
- Rapid onset of action.
- potent enough for use alone for short procedures
- Used with or without inhalational agent
- Large doses = hypotension/respiratory depression
- Crosses BBB = brain, redistributed to other tissues
2. Benzodiazepines

- **Midazolam & Diazepam**
- Too slow in onset to be of use in induction of anesthesia
- Used as premedication and as part of anesthetic mixtures
- Alone cannot produce surgical anesthesia (level 3) but can produce useful *anterograde amnesia* (patient will not remember they are about to have surgery)
- Slow recovery from anesthesia but a benzodiazepine antagonist, *Flumazenil*, can be used to speed recovery.
3. Opioids

- **Fentanyl, Sufentanil, Alfentanil, Remifentanil**
- Work through $\mu$-, $\kappa$-, $\delta$-opioid receptors
- Disadvantages: respiratory depression, Post-operative recall
- **Naloxone** or **Naltrexone** can be used during recovery
- Common combination: **Fentanyl + Thiopental**
4. Others

**I. Propofol**

- Important, rapid onset and offset
- Post-operative vomiting uncommon, patients ‘feel better’ in post operative period.
- Rapidly metabolized in liver
- Large doses = hypotension/respiratory depression
- Causes acidosis in children
- Expensive
II. *Etomidate*

- Rapid onset, used for induction, loss of consciousness within seconds
- Minimal cardiovascular and respiratory depression
- No analgesic effects
- It should be avoided in patients at risk of having adrenal insufficiency,
- more likely to cause involuntary movements during induction, postoperative nausea and vomiting, and pain at the injection site.
III. Ketamine

• Dissociative anesthesia: a state characterized by immobility, amnesia, analgesia with light sleep and feelings of dissociation from ones own body/mind
• Catatonia, no loss of consciousness
• Cardiovascular stimulation
• Useful for geriatrics, children and burn dressings
• Glutamate/NMDA receptor antagonist
• Unwanted effects: hallucinations and nightmares
Inhalation General Anesthetics
Inhaled Anesthetics

- Halothane
- Enflurane
- Isoflurane
- Desflurane

Halogenated compounds:
- Contain Fluorine and/or Bromide
- Simple, small molecules
INHALATION ANAESTHETICS

• Older agents: *Ether, Chloroform, Trichloroethylene, Cyclopropane, Methoxyflurane and Enflurane.*

• New agents: *Isoflurane, Sevoflurane and Desflurane.*

• Of the older agents, *Nitrous oxide* is still used widely (obstetric practice), and *Halothane* now only occasionally.

• Inhalation anaesthetics are most commonly used for the maintenance of anesthesia.
Mechanism of action:

- Activate $K^+$ channels
- Block $Na^+$ channels
- In general, all general anesthetics increase the cellular threshold for firing, thus decreasing neuronal activity.
• Nitrous oxide:
  – low potency, therefore must be combined with other agents
  – rapid induction and recovery
  – good analgesic properties
  – risk of bone marrow depression with prolonged administration
  – accumulates in gaseous cavities.
• **Halothane:**
  – no longer widely used
  – potent, non-irritant
  – may cause hypotension and dysrhythmias; about 30% metabolised
  – can be useful when slow recovery is desirable but otherwise the 'hangover' due to high lipid solubility is unwanted
  – risk of liver damage if used repeatedly in susceptible individuals.
• **Enflurane:**
  – halogenated anaesthetic similar to halothane
  – less metabolism than halothane, therefore less risk of toxicity
  – faster induction and recovery than halothane (less accumulation in fat)
  – risk of epilepsy-like seizures.
• Isoflurane:
  – similar to enflurane but lacks epileptogenic property
  – may precipitate myocardial ischaemia in patients with coronary disease
  – irritant to respiratory tract.
• **Desflurane:**
  – similar to isoflurane but with faster onset and recovery
  – respiratory irritant, so liable to cause coughing and laryngospasm
• Sevoflurane:
  – similar to desflurane, with lack of respiratory irritation.
• Some halogenated anaesthetics (especially halothane and Methoxyflurane) are metabolized. This is not very important in determining their duration of action, but contributes to toxicity (e.g. renal toxicity associated with fluoride production with Methoxyflurane--no longer used).
Toxicity of inhalation anesthetics

1. Nephrotoxicity: F- from hepatic metabolism

2. Hepatotoxicity (not much of a problem with modern drugs)
3. Malignant hyperthermia:

- Rare, genetically susceptible.
- Tachycardia, hypertension, hyperkalemia, muscle rigidity, and hyperthermia.
- Due to massive release of Ca^{++}
- Treat with *Dantrolene (Dantrium)*, lower elevated temperature, and restore electrolyte imbalance
ADJUNCTS TO ANESTHESIA

• Several nonanesthetic agents are used as adjuncts or supplements to anesthetic drugs.
  1. Antianxiety Agents
  2. Sedative-Hypnotics
  3. Anticholinergics
  4. Opioid Analgesics
  5. Neuromuscular Blocking Agents
• **These may include:**

1. A sedative or anxiolytic premedication (*Midazolam*)
2. An intravenous anaesthetic for rapid induction (*Propofol*)
3. A preoperative opioid analgesic (*Remifentanyl*)
4. An inhalation anaesthetic to maintain anaesthesia during surgery (*Isoflurane*),
5. A neuromuscular blocking agent to produce adequate muscle relaxation (*Vecuronium*)
6. An antiemetic agent (*Ondansetron*)
7. A muscarinic antagonist to prevent or treat bradycardia or to reduce bronchial and salivary secretions (*Atropine*)
8. An anticholinesterase agent (*Neostigmine*) towards the end of the procedure, to reverse the neuromuscular blockade.
9. An analgesic for postoperative pain relief (e.g. an opioid such as *Morphine* and/or a non-steroidal anti-inflammatory drug such as *Diclofenac*).
• Such combinations of drugs result in much faster induction and recovery, avoiding long (and potentially hazardous) periods of semiconsciousness, and it enables surgery to be carried out with less undesirable cardiorespiratory depression.
LOCAL ANESTHESIA
Outline

• History.

• Chemical Classes.

• Mechanism Of Action.

• Pharmacological Effects And Toxicities.

• Routes Of Administration.
History
Mechanism of action

- conduction of nerve impulses is mediated by action potential (AP).

- Cationic form of anesthetic binds at inner surface of Na+ channel – preventing Na+ influx (rising phase of membrane potential) which initiates AP → blockade of nerve impulses (e.g., those mediating pain)
"Schematic" Action Potential

- Membrane Voltage (mV)
- Time (ms)
- Threshold
- Failed Initiations
- Resting Potential
- Undershoot
- Stimulus
- Peak
- Rising Phase
- Falling Phase
- Overshoot
Extracellular Area

LA

Na⁺

Sodium channel

Axonal membrane

LA receptor

Intracellular Area
## Chemical classes

### Pharmacology Of Local Anesthesia

### Contrast between ester & amide groups

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<tr>
<th>Features</th>
<th>Esters</th>
<th>Amides</th>
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<tr>
<td>Chemical bond</td>
<td>Ester bond</td>
<td>Amide bond</td>
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<tr>
<td>Common example</td>
<td>Procaine (Novocaine)</td>
<td>Lidocaine (Xylocaine)</td>
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<td>Allergy</td>
<td>Low</td>
<td>Very low</td>
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<tr>
<td>Metabolism in</td>
<td>Plasma pseudo-cholinesterase enzyme</td>
<td>Liver microsomal enzymes</td>
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<td>AMIDE GROUP</td>
<td>ESTER GROUP</td>
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<td>Lidocaine</td>
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<td>Prilocaine</td>
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Pharmacological effects and toxicities

- **Functional consequences of Na+ channel blockade by local anesthetics:**
  - **nerves:** decrease or abolition of conduction
  - **vascular smooth muscle:** vasodilatation
  - **heart:** decreased excitability (reduced pacemaker activity, prolongation of effective refractory period)
  - **CNS:** increased excitability, followed by generalized depression
• Anesthetic-induced vasodilatation can be counteracted by the concomitant administration of a vasoconstrictor.

• consequences of including vasoconstrictor:
  – prolongation of anesthetic action
  – decreased risk of toxicity
Applications of local anesthesia

1. NERVE BLOCK: injected locally to produce regional anesthesia (e.g., dental and other minor surgical procedures).

2. TOPICAL APPLICATION: to skin for analgesia (e.g., Benzocaine) or mucous membranes (for diagnostic procedures)
COW-GATES BLOCK
3. **SPINAL ANESTHESIA**: injection into CSF to produce anesthesia for major surgery (e.g., abdomen) or childbirth.

4. **LOCAL INJECTION**: at end of surgery to produce long-lasting post-surgical analgesia (reduces need for narcotics).

5. **I.V. INFUSION**: for control of cardiac arrhythmias (e.g., Lidocaine for ventricular arrhythmias).
thoracic spine

lumbar spine

sacrum

spinal cord
dura mater
epidural space
spinal space (subarachnoid space) containing cerebrospinal fluid
epidural anaesthesia
spinal anaesthesia
nerve fibres

area of injection
Local Anesthetic Toxicity

- manifestations of local anesthetic toxicity: *allergic reactions, cardiovascular and CNS effects*
• **allergic reactions:** restricted to esters—metabolized to allergenic p-amino benzoic acid (PABA) (∴ amides usually preferred for nerve block)

• **CVS:** may be due to anesthetic(cardiodepression, hypotension) or vasoconstrictor(hypertension, tachycardia) ⊸ monitor pulse/blood pressure

• **CNS:** excitability(agitation, increased talkativeness –may → convulsions) followed by CNS depression.
Don't Forget...
MIDAZOLAM
PROPOFOL
Etomidate Injection
20 mg per 10 mL
(2 mg per mL)
For Intravenous Use
10 mL Single-Dose Vial
Isoflurane USP
99.9%
LIDOCAINE
BUPIVACAINE

Bupivacaine HCl Inj., USP
0.5% (5 mg/mL)

For NERVE BLOCK, CAUDAL, and EPIDURAL ANESTHESIA.
Not for spinal anesthesia.

HOSPIRA, INC., LAKE FOREST, IL 60045 USA

30 mL Single-dose
Preservative-Free

Lot 80-477-DK EXPIRY

Rx only
THAT'S THE END

IF YOU HAVE ANY QUESTIONS PLEASE FEEL FREE TO ASK??
Thanks!

Thanks for your attention